UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,497	09/15/2003	Jennifer Jones McIntire	STAN-235CIP	2319

24353 7590 03/05/2008

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
03/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/663,497	MCINTIRE ET AL.	
	Examiner	Art Unit	
	SARAE BAUSCH	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/31/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8 and 20-23* is/are pending in the application.

4a) Of the above claim(s) *2 and 3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 7-8, 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

2. Currently, claims 1-4, 7-8 and 20-23 are pending in the instant application. Claims 5-6 and 9-19 have been canceled. Claims 2-3 are withdrawn. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented or are reiterated from the previous office action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Non-Final**

Withdrawn Rejection

3. The rejections of claims 8 and 20-22, under 35 U.S.C. 112, 1st paragraph, made in section 8, of the previous office action mailed 10/04/2007 is withdrawn in view of the amendment to the claims.

Maintained Rejections

Claim Rejections - 35 USC § 112- New Matter

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is newly presented, necessitated by the newly added claim. This rejection was previously presented in section 5 and is reiterated below.

Newly amended claim 23 with the recitation of "a probe that specifically binds under stringent conditions to polymorphisms in exon 3 of TIM-1 gene" is not supported in the specification and raises the issue of new matter. The specification teaches four polymorphisms within exon 3 of TIM-1, SEQ ID No. 37-40 (see paragraph 37, page 9). The specification teaches hybridization patterns of variant sequences using oligonucleotide probes immobilized on a solid support (see paragraph 56, page 14) and teach hybridization under stringent conditions (see paragraph 57, page 15). The specification teaches the arrays may comprise probes specific for one two three or more TIM alleles, TIM-1, TIM-2, TIM-3, TIM-4 or combination thereof and teach the probes specifically bind to the allele of interest (see paragraph 59, page 15), however the specification does not teach probes specific for "any" polymorphism in exon 3 of the TIM-1 gene, to which the claim is drawn. The specification only teaches four polymorphism within exon 3 of the TIM-1 gene and does not teach probes that specifically bind to any other polymorphism within exon 3. The specification does not provide support for a probe that hybridizes under stringent conditions to polymorphisms in exon 3 of the TIM-1 gene. There is

no support in the specification to use a probe to specifically bind to any polymorphism within exon 3 of TIM-1 gene.

Response to Arguments

6. The response traverses the rejection on page 6 of the remarks mailed 10/31/2007. The response assert that the amendment to claim 23 addresses the rejection. The response further states on page 5 of the remarks mailed 10/31/2007 that support for the term "probes" is found on page 15, paragraph 59. This response has been thoroughly reviewed but not found persuasive. The amendment to claim 23 to recite probes that bind to polymorphisms in exon 3 of TIM-1 gene does not overcome the rejection. The claim is broadly drawn to detecting any polymorphism within exon 3 and the specification provides support for only 4 polymorphisms located within exon 3 of TIM-1. The recitation of "probes that bind to polymorphisms in exon 3 of TIM-1 gene" broadens the scope of the claim and the specification does not support this generic scope. Furthermore, the examiner agrees that the specification provides support for the term "probe" however the specification does not provide support for a probe that hybridizes to any other polymorphism other than the four polymorphisms of exon 3 disclosed in the specification. Page 15, paragraph 59, provides support for probes, probes utilized in array, types of arrays. Furthermore, paragraph 59, page 15 states "it will be desirable for probes to specifically bind to the allele of interest", however this passage does not provide support for probes that bind to exon 3 of TIM-1 gene. The specification does not contemplate the use of probes for detection of multiple polymorphism within exon 3 of TIM-1 gene other than the four polymorphisms disclosed in the specification. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 112-Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 4, 7-8 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for determining a Caucasian or Asian's predisposition to atopy protection by detecting the presence of homozygous polymorphism of 157insMTTTVP (polymorphism 1, SEQ ID No. 22), of TIM-1 in a hepatitis virus A positive Caucasian individual, wherein the presence of the MTTTVP insertion is indicative of a Caucasian's predisposition to protect against atopy, does not reasonably provide enablement for a method for screening for a human individual's predisposition to any atopy by analyzing for the presence of any TIM-1 polymorphism. This rejection was previously presented in section 7 of the previous office action mailed 10/04/2007 and has been rewritten.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the screening for a human individual's predisposition to atopy by analyzing the presence of at least one TIM-1 polymorphism wherein the presence of the polymorphism is indicative of an individual's predisposition to develop an atopy. The claims are further drawn to a method of contacting a biological sample with a probe that specifically binds to the nucleic acid sequence of MTTTVP or a polymorphism in exon 3 of TIM-1 gene and further comprising the step of analyzing an individual for the presence of hepatitis A virus seropositivity.

The rejected claims encompass analysis of a human. The rejected claims encompass any type of atopy and detection of any polymorphism in TIM-1.

The nature of the claims requires knowledge of a correlation between detection of the presence of a TIM-1 polymorphism and predisposition to develop atopy.

Guidance in the Specification and Working Examples

The specification asserts that polymorphisms in the human TIM-1 gene and exposure to Hepatitis A Virus(HAV) are shown to be associated with protection from the development of immunological disorders, such as atopy. The specification asserts that a common polymorphism of TIM-1 in major human population has an insertion at position 157, 157insMTTTVP and HAV seropositivity protects against atopy but only in individuals with 157 insMTTTVP allele. The

specification asserts that in some aspects the atopic disease is allergic rhinitis, atopic dermatitis, or asthma (see page 2, paragraph 6).

The specification asserts that polymorphisms in the coding region of human TIM1 include an insertion, 157insMTTTVP (allele 1), a deletion 195ΔThr, 157insMTTVP, T140A, V161A, V167I, T172A, and N258D (see paragraph 37, page 8-9) and assert that most of these variations are located within exon 3. The specification asserts that Tim gene sequence is other than human Tim-1, allele 1. The specification asserts that in combination with HAV seropositivity, allele 1 is protective for atopy and the presence is indicative that an individual may benefit from exposure to HAV for atopy treatment and/or prophylaxis and determination of the presence of the allele may be determined by various methods known in the art (see page 10, paragraph 42). Although determination of allele is routine in the art, predictably correlating an allele to atopy in any human individual is unpredictable and the specification does not predictably correlate each of these polymorphisms with atopy in any human individual.

The specification teaches there are a number of methods that are available for analyzing nucleic acid for the presence of a specific sequence. The specification teaches that amplification with detectable labels, oligonucleotide ligation, hybridization to any array are available (see paragraph 53-54, 56, pages 13-14). However, the specification does not predictably correlate a method for screening for predisposition to atopy in any human by detecting "any" polymorphism within the TIM-1.

The specification demonstrates a working example of association between atopy and 157insMTTTVP in a cross-sectional study of 375 individuals who were tested for serologic evidence of atopy and prior HAV infection. The specification demonstrates that HAV infection

protects against atopy but only in individuals with the 157insMTTTVP Tim-1 allele (see paragraph 194, pages 54-55). Although, table 1 of the specification demonstrates that HAV positive subjects with the 157insMTTTVP Tim-1 allele are associated with protection against atopy, table S3 and S4 demonstrate that 157insMTTTVP is predictably correlative for only the Caucasian population that is HAV positive and that are homozygous for the 157insMTTTVP allele. Table S4 demonstrates that neither the HAV negative or HAV positive population of Asians subjects is statistically relevant to diagnosis a predisposition to any immunological disorder or atopy and Table S3 demonstrates that the only statistically relevant data in the Caucasian subjects is for Caucasians subjects with HAV that are homozygous for 157insMTTTVP allele. The specification asserts that the African American sample size was too small to present separately (see paragraph 199, page 56).

The specification does not teach the association of any polymorphism, other than the 157insMTTTVP allele, in TIM-1 gene with the risk of developing atopy. The specification does not teach an association of any polymorphism with an increased likihood of developing atopy.

The following is unclear from the teaching in the specification. The specification does not teach which polymorphisms other than 157insMTTVIP allele of the TIM-1 gene is predictably correlative to diagnosing a predisposition to atopy in all ethnicities. The specification teaches only a statistically relevant association of 157insMTTTVP in Caucasian subjects that are homozygous for the allele that are HAV positive and have protection against atopy. The specification does not teach an association with any other polymorphism with TIM-1 and any atopy or association with presence or absence of HAV. It is unclear which polymorphism would be predictive of screening for predisposition to atopy in "any" individual.

The specification envisions hypothetical situations where any polymorphism within the TIM-1 gene could determine the presence of atopy. The specification appears to be conceiving of possible scenarios where the presence of any polymorphism in TIM-1 would indicate the presence – or absence – of atopy, however, it is unclear how one of skill in the art would determine which polymorphism of TIM-1 gene would screen for predisposition to atopy.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between any polymorphism in TIM-1 gene and predisposition in any individual for atopy.

While the claims of the instant application are broad and encompass analysis of any human, the instant specification provides evidence only of a statistically significant association between the 157ins MTTTVP allele of TIM-1 of SEQ ID No. 22, and protection against atopy in Caucasians that are positive for HAV.

Because the claims are drawn to methods that encompass the analysis of any polymorphism of TIM-1 gene, it is relevant to note that there are multiple polymorphic positions identified in TIM-1. A Gene Card search of TIM-1 gene indicates that there are 135 SNPs of TIM-1 gene (see page 7 of Gene Card). The instant specification does not teach any association of these 135 polymorphisms with atopy.

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more

family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph).

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$

should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the TIM-1 gene with atopy, as the specification does not teach a large sample size or confidence levels greater than 95% for every polymorphism of the TIM-1 gene or the association of TIM-1 with atopy. The specification only teaches a large sample size with statistically significant data for the analysis of an association between HAV positive subjects with the 157insMTTTVP allele in a Caucasian population.

Furthermore, the post filing art teaches the unpredictability of determining an association in different ethnical groups with any polymorphism in TIM-1 gene with atopy. Noguchi et al. (Genes and Immunity (2003) 4:170-173) teach that the seven different polymorphism within the TIM-1 gene, including two insertions and deletions were found not associated with the development of asthma in Japanese asthmatic families that showed strong evidence for linkage of atopic asthma (see page 172, right column, last paragraph). Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A

infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph).

Applicant's own post-filing art, Umetsu et al. (Ann NY Acad Sci, 2004, 1029:88-93), teach that in the total population there was no association of the TIM-1 insertion (157insMTTTVP) with atopy. Umetsu et al. teach that if an individual had one or two copies of the insertion polymorphism in TIM-1, he or she was as likely to be atopic as those who had no copies of the insertion polymorphism, however when assayed for HAV seropositive and seronegative, it was found that a significant inverse association of the insertion and atopy. Umetsu et al. teach that the HAV seropositive subjects who had one or two copies of the insertion were much less likely to be atopic that those who had no copies and the HAV negative population was no associated with any protection against atopy. (see page 92, 1st full paragraph). Thus, Umetsu et al. teach that the only individuals that are HAV positive are predictably correlative to protection against atopy in individuals that have the polymorphic insertion in TIM-1 gene.

Graves et al. (J Allerg Clin Immunol 2005, vol 118, pages 650-656) teach a study to evaluate multiple polymorphism in TIM1 gene and the association with atopy. Graves et al. teach association with atopy and one polymorphism, 15bp insertion/deletion of TIM-1 (see page 655, 1st column, 1st full paragraph). Graves et al. teach that in a Korean case control study increased risk for atopic dermatitis was found but not for asthma with the 15bp deletion of the TIM-1 gene (see page 655, 1st column, 1st full paragraph). Graves et al. teach analysis of seven different polymorphisms of TIM-1 gene and demonstrate that several polymorphisms are not

statistically relevant, for example TIM1_1, 2, 5, and 7 (see table E2). Graves et al. teach that their findings need to replicated in other studies and the major limitation of the analysis is related to ethnic heterogeneity reflected in the Tucson population. Therefore, Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed.

The claims are broadly drawn to screening for predisposition to any individual of atopy. The example presented in the specification provides an analysis of the 157insMTTTVP allele of TIM-1 gene with regard to HAV positive Caucasians subjects and atopy. The prior art teaches that confidence levels greater than 95% are necessary for predictably associating genetic tests with diseases. The instant specification shows the unpredictability in associating any polymorphism, including 157insMTTTVP allele of TIM-1 gene with any individual for any type of atopic immunological disorder. For example, table S3 demonstrates that 157insMTTTVP is not associated with atopy protection any individual that is not HAV positive and demonstrates that the 157insMTTTVP is not associated with atopy protection in every ethnic group (see table S4 and lack of African American analysis). Thus, based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the TIM-1 gene with any type of immunological disorder, as the specification does not teach a large sample size or confidence levels greater than 95% for every polymorphism of the TIM-1 gene or the association of TIM-1 with any type of immunological disorder. The specification teaches a large sample size with statistically significant data for the analysis of an association

between HAV positive subjects with the 157insMTTTVP allele in the TIM-1 in a Caucasian population for protection against atopy.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to association of any polymorphism in the TIM-1 gene with any atopic immunological disorder in any individual along with the evidence in the art that demonstrates that not every polymorphism of TIM-1 gene is associated with an immunological disorder, the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for each of the polymorphisms of the TIM-1 gene (135 polymorphisms known) to determine if in fact there was either an association between the polymorphism in individuals and atopy. The results of such a study are clearly unpredictable as evidence by the applicant's own post filing art (which reflects the current state of the art) and the teachings in the specification with regard to correlating the 157insMTTTVP allele of TIM-1 with different ethnic groups and HAV negative individuals to atopy much less any immunological disorder. Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed. Furthermore, Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph). In the instant case, it would be unpredictable as to whether or not

157insMTTTVP would be responsible for determining the predisposition to atopy in any individual without also determining if the individual was HAV positive or negative.

In order to practice the invention as broadly as it is claimed, the skilled artisan would have to determine the sequence of the human TIM-1 in each individual and then determine which polymorphism would detect any type of immunological disorder. The skilled artisan would then have to screen variants to determine those that are associated with a susceptibility to any atopic immunological disorder in all populations. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to all or any atopy. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Response to Arguments

9. The response traverses the rejection on pages 6-16 of the remarks mailed 10/31/2007. The response asserts on page 7, last paragraph cont'd to page 8 that the claims are drawn to method of screening at least one TIM-1 polymorphism where the presence of the polymorphism is indicative of individual's predisposition to develop atopy. The response asserts that a correlation between detection of the presence of a TIM- 1 polymorphism and predisposition to develop atopic immunological disorder is provided in the specification. The response states that common polymorphism in TIM-1 and linkage of TIM-1 locus to development of atopy can be found in the specification. This response has been thoroughly reviewed but not found persuasive. The specification teaches 7 polymorphisms (paragraph 37) however the specification does not teach an association between these 7 polymorphisms and atopy. The specification only

provides a predictable association between HAV (+) and 157insMTTTVP polymorphism in a Caucasian population. The specification does not provide any analysis of representative number of polymorphisms with atopy other than 157insMTTTVP.

The response states on page 8, that numerous publication have corroborated the correlation between the detection of the presence of TIM-1 polymorphism and predisposition to atopy. The response points to post filing art to demonstrate that the correlation between TIM-1 polymorphism and atopy. It is noted that the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. The publications relied upon by applicants are post filing publications and are therefore not evidence of the state of the art at the time of filing. With respect to the individual references relied upon by applicant, it is noted that Graves et al. teach that their findings need to be replicated in other studies (See pg. 655, 2nd column, last para). Furthermore, Graves et al. analyze only one polymorphism within TIM-1 a 15bp insertion (see pg.655, 1st column, 1st full para), which is not disclosed in the present specification. Additionally, Sizing et al. teach that in 2007 the TIM-1 locus was linked to atopic disease (see abstract). Sizing et al. does not teach analysis of polymorphisms within TIM-1 gene and atopy in humans, as Sizing et al. analysis was demonstrated in mice not humans (See pg. 2251), therefore Sizing et al. can not be relied upon to corroborate the correlation between the presence of TIM-1 polymorphisms and predisposition to atopy in humans at the time of filing.

The response asserts that the claims do not encompass correlating the presence of a polymorphisms to the development atopy but rather encompass presence of a polymorphism being indicative of the individual's predisposition to develop atopy. The response state that

applicants are not claiming every polymorphism in TIM-1 is related to atopy and are limiting the claims to method of detecting polymorphisms in TIM-1. This response has been thoroughly reviewed but not found persuasive. It is noted that claims are not limited to a method of detecting a polymorphism in TIM-1 gene. The claims are drawn to a method of screening an individuals predisposition to atopy by analyzing the presence of the TIM-1 polymorphism. The claims require the presence of a polymorphism that is indicative of atopy. Furthermore the examiner maintains that the claims require that there is a correlation between the presence of a polymorphism in TIM-1 gene and atopy, be in development of atopy, predisposition to atopy, etc. the claims still require a correlation between polymorphisms in TIM-1 gene and atopy. The claims are not limited to specific polymorphisms and recite at least one polymorphism in TIM-1 and therefore broadly encompass any polymorphism in the TIM-1 gene.

The response states on page 9 that the claims do not recite that every polymorphism in TIM-1 is related to an atopic disorder. The response asserts that the claims are limited to detecting polymorphisms in TIM-1 gene, which information is useful to an individual wishing to evaluate their predisposition to atopy and further evaluated in the context of HAV-1 seropositivity. The examiner agrees that the claims do not recite that every polymorphism in TIM-1 is related to atopic disorder however the claims encompass any TIM-1 polymorphism is associated with atopy. The specification does not disclose a representative number of polymorphisms predictably associated with atopy. Furthermore, the claims are not limited to a method of detecting polymorphisms in TIM-1 gene, the claims are drawn to a method of screening for a human's individual predisposition to atopy and therefore the claims encompass the analysis that a TIM-1 polymorphism is predictably associated with atopy.

The response asserts that the instant specification demonstrates that TIM-1 gene is associated with atopy and the constructive reduction to practice constituted by the present application provides a rationale for the selection of the TIM-1 gene as a screening tool for atopic disorders and means to effect such screening. It is noted that the claims are not limited to a method of screening for a TIM-1 gene, the claims require the knowledge that a specific polymorphism is associated with atopy. The specification does not teach a representative number of polymorphisms associated with atopy. Furthermore, the association of the TIM-1 gene with atopy does not provide a reduction to practice for polymorphisms within the TIM-1 gene. The post filing art teaches that even if a gene is associated with involvement of a disorder does not reason that a polymorphism within the gene with also be associated with a disorder (See Hattersly and Hegele above).

The response asserts that since the specification provides atopic conditions of interest, detailed description of TIM gene family, molecular characteristic of TIM gene products, references linking the TIM gene family to multiple atopic disorders, description of the important role of the TIM-1 gene in immunological response, methods of isolating TIM gene from tissue samples, techniques for genotyping TIM alleles and typical methods of preparing and detecting probes, the specification provides everything that is needs such that the ordinary skilled artisan can identify polymorphic allelic variants of TIM-1 associated with atopic conditions and use such polymorphisms for diagnostic purposed. The response asserts that thus the specification supports constructive reduction to practice for any TIM-1 allele by the present application. This repose has been thoroughly reviewed but not found persuasive. This response has been thoroughly reviewed but not found persuasive. Proof of constructive reduction to practice

requires sufficient disclosure under 35 USC 112, 1st paragraph, how to use and how to make. In the instant case, the specification does not provide sufficient disclosure for a representative number of polymorphisms within the TIM-1 gene and their association to atopy disorder. Furthermore, although the specification does disclose molecular characteristic of the TIM-1 gene and TIM gene family, this does not teach how to make and use the claimed invention. For example, the specification does not disclose a representative number of alleles within the TIM-1 gene that are predictably associated with atopy. As taught by the post filing art, SNP association is unpredictable and requires large sample sizes and analysis of each polymorphism. As such, the specification is not enable for any polymorphism within the TIM-1 gene to be predictably associated with atopy and therefore the specification does not provide proof of constructive reduction to practice. Furthermore, as stated above, while identifying polymorphic allelic variants of a gene is routine in the art, the ability to predictably correlate the polymorphic variants with a disease is unpredictable. In the instant case, the specification is suggesting the role of TIM-1 in immunological response and atopic disease and suggesting that polymorphisms within this gene may be associated with an atopic disease, however the specification does not provide evidence that polymorphisms within TIM-1 gene in any population are associated with atopic disease. The specification asserts an association of one polymorphism with the TIM-1 gene with protection against atopy however the specification does not demonstrate the presence of a polymorphism within the TIM-1 gene and predisposition to developing atopy.

The response asserts on page 10 that both the Caucasian and Asian population the 157insMTTTVP 1,2 vs. 0 allele reports a significant P value for HAV + individuals and therefore 157insMTTTVP is predictably correlative for the group including seropositive

heterozygous and homozygous individuals. This response has been thoroughly reviewed but not found persuasive. The column 1,2 vs 0 allele is for "1 or 2 copies" of 157insMTTTVP polymorphism, column 2 vs 0 allele is analysis of 2 copies of the polymorphism (homozygous), and the column 1 vs 0 allele is analysis of one copy of the polymorphism (heterozygous). Table S4 demonstrates that analysis based solely on either heterozgosity or homozgosity (one or two copies) 157insMTTTVP is not predictably associated with atopy in HAV + in the Asian population. It is unclear how column 1,2 vs 0 allele is statistically significant when the analysis of the one copy or two copy alone does not provide statistically significant data. It is unclear what this data represents, hence the conclusion of the examiner that the data in table S4 is not statistically significant as it appears that column 1,2 vs 0 allele is the combination of the other two columns within table S4 and its unclear how this column has a p value that is .036 while the other two analyses have a p value of .096 and .113.

The response asserts that the lack of presentation of a subgroup analysis of African American individuals is solely to the small n value of the group. The response asserts that the table 1 was performed with racial stratification and the statistical conclusion is valid for all included ethnicities. This response has been thoroughly reviewed but not found persuasive. The specification provides evidence that 157insMTTTVP allele is not predictably associated with atopy in either Caucasians or Asians, much less African Americans and provides no evidence of other polymorphisms associated with atopy. Therefore, the specification demonstrates that confirming the finding of an association of a polymorphism with a disorder will not necessarily be confirmed in subpopulations and demonstrates the unpredictability of associating the presence

of any polymorphism within the TIM-1 gene to predisposition to develop atopic immunological disorder.

The response asserts that numerous polymorphism in TIM-1 gene and the linkage of TIM-1 gene to atopy are described in the specification. It is noted that the specification discloses seven polymorphism within the TIM-1 gene. The response further asserts that the instant application does not recite nor imply that every polymorphism of TIM-1 will carry predictive association with atopic disease. This response has been thoroughly reviewed but not found persuasive. It is noted that the examiner agrees that not every polymorphism need to carry a predictive association with atopic disease, however a representative number of the large genus claimed need to be predictably associated with atopy. The examiner also agrees that neither the specification nor the claims require that every polymorphism is associated with atopy, however the claims are not limited to a specific polymorphism within the TIM-1 gene and therefore encompass *any* polymorphism with the TIM-1 gene.. Furthermore the claims are not drawn to a screening or assaying method to determine *if* a polymorphism is associated with atopy, the claims require the knowledge of the association of a polymorphism within TIM-1 gene and atopy and the specification does not enable the skilled artisan to associate polymorphisms within the TIM-1 gene and atopy. The specification provides analysis of only one, 157insMTTTVP and demonstrates that this polymorphism is not predictably associated with atopy therefore the specification does not demonstrate a single species of the large genus of polymorphisms that are predictably associated with atopy.

The response asserts on page 11 that numerous post filing art describe the predictability of associating polymorphisms in TIM-1 gene with predisposition with atopic disorder. The

response asserts that Chae demonstrate variations in TIM-1 gene are associated with asthma in Korean population. It is noted that although Chae demonstrate one polymorphism is associated with asthma, Chae demonstrate that another variant, 5383_5397del was not associated (see table 1) and therefore demonstrates that not any polymorphism within TIM-1 is predictably associated with atopy. Furthermore, Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed. Additionally, Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph) (see rejection above). Therefore, the evidence in the art coupled with the evidence in the specification demonstrates the unpredictability of associating any polymorphism in the TIM-1 gene with predisposition to developing an atopic immunological disorder in an individual.

The response asserts that association of polymorphisms in TIM-1 gene and predisposition to atopy have been described in the specification and numerous publications. This response has been thoroughly reviewed but not found persuasive. The prior art demonstrates the unpredictability of associating polymorphisms in TIM-1 gene with atopy as there are multiple publications that demonstrate that not all polymorphisms within TIM-1 gene are predictably associated with atopy. Furthermore the specification does not provide a single working example of a polymorphism within TIM-1 gene that is predictably associated with atopy that is not

associated with HAV seropositivity. Example 6 provides evidence of homozygous 157MTTTVP polymorphism within TIM-1 gene is predictably associated in Caucasian population that are HAV (+).

The response asserts that techniques for generating probes with specificity for any TIM-1 alleles are routine in the art. This response has been thoroughly reviewed but not found persuasive. The examiner agrees the techniques for generating probes with specificity for TIM-1 alleles is routine in the art. However, the claims are not drawn to a method of analyzing the TIM-1 sequence. The claims are drawn to a method of diagnosis a human individual's predisposition to an atopic immunological disorder by analyzing a polymorphism for the presence of a TIM-1 polymorphism. As such the claims require the knowledge of an association of polymorphism within the TIM-1 gene and atopic immunological disorders. The specification does not evaluate any TIM-1 polymorphism other than 157insMTTTVP and its association with atopic immunological disorders in an individual.

The response asserts that the teaching of Kroese are fulfilled by the claimed method. The response states the findings of the exemplified reduction to practice the association of protection from atopy with 157insMTTTVP allele in the presence of HAV seropositivity is presented with p values >95% confidence as shown in table 1. It is noted that the exemplified reduction to practice does not demonstrate >95% confidence intervals for atopy and 157insMTTTVP, only for 157insMTTTVP homozygous allele in a population with HAV (+) Caucasian subjects (see table S3 and S4). The specification does not teach analysis of any other polymorphism and thus does not demonstrate >95% confidence intervals for polymorphisms in the TIM-1 gene and association with atopy.

The response addresses the recommendations of Lucentini on page 15 and assert the population displaying atopic conditions is large and diverse as evidence in the present specification and assert that the likihood of founder effects is small and the likihood of such effects reducing the informatively of the data in a study comprising multiple ethnic groups is small and the recommendations of Lucentini are satisfied with respect to the instant specification. It is noted that although the population is large and diverse that is presented in the specification, the data presented in the subpopulation findings in the specification demonstrates that unpredictability of associating a polymorphism with atopic immunological disorder in any population. The critical findings demonstrated in table S3 and S4 demonstrate that the polymorphism is not associated with atopic immunological disorder in every population, as both Caucasians and Asians that are not HAV + who carry either the homozygous or heterozygous allele 157insMTTTVP furthermore the specification does not demonstrate a population of individuals with the 157insMTTTVP and their predisposition to develop atopy. The specification demonstrates that the recommendations of Lucentini suggesting a large, more diverse sample size is necessary to demonstrate an association with a gene and disorder as the large study presented in the specification demonstrates that subpopulations, those that are HAV negative and different ethnic groups will not have a protection against developing atopy with the presence of the polymorphism 157insMTTTVP.

The response addresses Noguchi et al. on page 13-14. The response asserts that none of the polymorphisms identified by Nogushi were associated with asthma in the present experimental examples. The response further asserts that there is no contradiction between the results of Noguchi and those of the present example because the individuals assayed in the

specification was for individuals answering calls for allergic reactions not for familial asthma. The response asserts that it is nowhere implied or recited that every polymorphism in TIM-1 must carry predictive association with an atopic disease and the claimed method relies on techniques well known in the art to assess association of a polymorphisms with atopy. This response has been thoroughly reviewed but not found persuasive. It is noted that the claims are drawn to the presence of analyzing a polymorphism within the TIM-1 gene and the presence of a polymorphism is indicative of developing atopic immunological disorder. The claims are drawn to atopy, which encompasses asthma including familial asthma and are drawn to the association of any polymorphism with the TIM-1, which encompasses the polymorphisms taught by Noguchi. It is noted that claim 1 and 7 recite "at least one TIM-1 polymorphism" and therefore encompass any polymorphism within the TIM-1 gene. Noguchi et al. demonstrates the unpredictability of associating any polymorphism in the TIM-1 with atopic immunological disorder. Noguchi et al. demonstrates polymorphisms in TIM-1 are not associated with asthma and further demonstrates that different populations are needed to elucidate the role of TIM-1 polymorphisms in atopic diseases (see pg. 172, 2nd column, last paragraph). Therefore, Noguchi et al. demonstrates that some polymorphism within TIM-1 are not associated with atopy, such as asthma.

The response addresses Umetsu et al. on page 14. The response asserts Umetsu et al. confirm the results presented in the specification and there is no apparent contradiction between the result of Umetsu et al. and those of the present examples. The response further asserts that there is no a prior reason that viral infection should be excluded from individuals suffering atopy in whom the method finds use. This response has been thoroughly reviewed but not found

persuasive. Umetsu provides evidence that individuals that are HAV negative are not associated with atopy (see pg. 92, 1st full paragraph). The claims are drawn to diagnosing any human for atopy by detecting the presence of a polymorphism in TIM-1. Claims 1, 4, 7, 20 and 23 are not limited to the population being HAV + or - and the specification demonstrates the unpredictability of associating any population with any polymorphism with atopy and Umetsu et al. provides further evidence of the unpredictability of associating any individual with atopy. With regard to applicants assertion that there is no a priori reason that viral infection should be excluded from individuals suffering atopy, in the instant case the presence of HAV is the only population demonstrated in the specification to be associated with atopy and 157insMTTTVP polymorphism. Furthermore, as stated above although the claims do not require that every polymorphism is associated with atopy however the claims recite "at least one TIM-1 polymorphism" are not limited to specific polymorphisms and therefore broadly encompass any polymorphism within TIM-1 gene.

The response addresses Graves et al. on page 14-15. The response asserts that none of the polymorphisms identified as not significantly associated with atopy by Graves et al. were found to be associated with atopy in the present examples and it is not recited or implied that every polymorphism of TIM-1 must carry predictive association with an atopic disease. This response has been thoroughly reviewed but not found persuasive. As stated above, claim 1 and 7 are broadly drawn to "at least one TIM1 polymorphism" and are not limited to specific polymorphisms and therefore the claims are broadly drawn to "any" polymorphisms within TIM-1 gene, which encompasses the polymorphisms studied by Graves et al. Graves et al. demonstrates that polymorphisms within TIM1 gene are not predictably associated with atopy.

The response further asserts that Graves teach although a limitation of the analysis is reflected in the ethnic heterogeneity of the Tucson population similar results were replicated in children with two Caucasian parents, indicating significant association are unlikely to be related to population stratification as the result of ethnicity and the response asserts that the study does not cast doubt upon but rather substantiates the rationale and feasibility of the claimed method. This response has been considered but not found persuasive. Graves et al. asserts that their findings need to be replicated in other studies (see page 655, 1st column, last paragraph), which demonstrates their doubt on the results of the study and does not substantiate the rationale or feasibility of the claimed method. Furthermore, Graves et al. teach several different polymorphisms within TIM-1 gene that were not statistically relevant and not associated with atopy (see table E2) and further demonstrate that the 15bp deletion of the TIM-1 gene (see pg. 655, 1st column, 1st paragraph) was not associated with asthma but was associated with atopic dermatitis, which demonstrates the unpredictability of any atopy immunological disease and a polymorphism within the TIM-1 gene. Therefore, Graves et al. demonstrates the unpredictability of associating any polymorphism within TIM1 gene with atopic immunological disorder.

The response asserts on page 15, Gao et al. demonstrates that 157delMTTTVP were higher among patients with asthma compared with controls. The response asserts that Gao et al. demonstrate TIM 1 allelic variation is stasticially associated with atopic conditions in African American population. This response has been thoroughly reviewed but not found persuasive. Gao et al. demonstrate that African Americans that do not have the MTTTVP (see table II and pg. 987, 1st column, last paragraph) insertion are predictability associated with asthma which is the opposite of the claimed method. The claims are drawn to the presence of a polymorphism is

associated with an individual predisposition to atopic immunological disorder (claim 1) and further limited to detecting the presence of MTTTVP. Therefore the claims are drawn to associating the insertion of MTTTVP with predisposition to atopic immunological disorder, whereas the teaching of Gao et al. teach that the deletion, not insertion of MTTTVP is associated with African American population and asthma (see pg. 987, 1st column, last paragraph). Furthermore, Gao et al. demonstrate that HAV seronegative population and the insertion variant is marginally associated with asthma (see pg. 985, 2nd column, last paragraph) which demonstrates the polymorphism is not statistically associated with atopy. Therefore Gao et al. provides evidence of the unpredictably of associating a polymorphism within TIM1 with atopic immunological disorder.

The response asserts on page 16 that only experiments that need to be performed to enable the entire scope of the claim are those designed to assess the association of TIM-1 polymorphism with an atopic condition in a population of interest. The response asserts that the experimentation is routine. The response asserts that the only experimentation required to enable the claimed method is to confirm a statistical association of an allele in a population and this requires routine assay to determine and no undue experimentation is necessary. This response has been thoroughly reviewed but not found persuasive. As stated above, while identifying polymorphic allelic variants of a gene is routine in the art, the ability to predictably correlate the polymorphic variants with a disease is unpredictable. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant

specification, one skill in the art would have to engage in unpredictable, excessive and undue amount of experimentation to exercise the invention as claimed.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 112-Written Description

10. Claims 1, 4, 7 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was previously presented in section 8 of the office action mailed 10/04/2007 and is reiterated below.

> Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The rejected claims are broadly drawn to methods for diagnosing predisposition to any atopic immunological disorder comprising determining any polymorphism in any individual (claim 1). The claims are broadly drawn to methods comprising the detection of a variety of nucleic acids, including any polymorphic variant of TIM-1 gene that is associated with any type of atopy. The claims are limited to probes that specifically bind to exon 3 of TIM-1 gene (claim 23) or probes that bind to MTTTVP sequence (claim 4), however the limitation of probes that specifically bind to a nucleic acid sequence or exon 3 does not limit the claims to detection of a specific polymorphism of TIM-1 gene as the claims merely require analyzing a biological

sample with a probe that specifically binds to a nucleic acid sequence and this does not limit the polymorphism that is indicative of atopic immunological disorder. The claims merely require analyzing a probe that binds to a nucleic acid but the claims do not require the presence of the specific probe binding to the nucleic acid is indicative of predisposition to develop an atopic immunological disorder.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis and detection of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to a method that encompass a plurality of nucleic acids an extremely large genus of polymorphic variants of the TIM-1 gene with any nucleotide content (A or G or C or T) at any position within the TIM-1 gene. Thus the claims encompass the detection of any of different nucleic acids wherein the nucleic acid sequence is correlated with an association of disease. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of SEQ ID No. 18, 20, 22, 24, 26, and 28. The specification also provides the amino acid sequence of TIM-1 as SEQ ID No. 19, 21, 23, 25, 27, and 29. The specification provides analysis of the insertion of the following amino acid sequence of MTTTVP at position 157 and indicating that this insertion is indicative of association of disease. The specification does not teach any association with any other polymorphic variation disclosed in the specification, for example deletion 195ΔThr,

157insMTTVP, T140A, V161A, V167I, T172A, and N258D that are indicative of association of atopic immunological disorders.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the polymorphic sequences of the human TIM1 gene (SEQ ID NO: 18, 20, 22, 24, and 26) and the encoded amino acid sequence (SEQ ID NO: 19, 21, 23, 25, 27). The specification does not provide any characteristics that would allow one to identify any other genes from another organism or any particular portions or fragments or variants of the disclosed sequence that would allow for the diagnosis of any type of atopic immunological disorder based on detection of the non-disclosed gene. Furthermore, the art discloses that there are 135 SNPs known for the TIM-1 gene (see GeneCard, page 7). Neither the specification nor the prior art teach an association with any of these SNPs with any type of immunological disorder or atopy.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding polymorphisms of

the TIM-1 gene other than the insertion of the amino acid sequence of MTTTVP at position 157 of the amino acid sequence, one of skill in the art cannot envision the detailed chemical structure of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method of diagnosis for the predisposition of immunological disorder in an individual by determining the presence of a polymorphism in TIM-1 other than methods using detection of the insertion of the amino acid sequence MTTTVP at position 157 of TIM-1.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Arguments

11. The response traverses the rejection on pages 17-18 of the remarks mailed 10/31/2007. The response asserts that the claims are drawn to detecting polymorphisms specific to TIM-1 and not to any polymorphism as stated by the examiner. It is noted that the examiner did not state that the claims are drawn to detecting any polymorphism. The examiner stated (see above) that the claims encompass a plurality of nucleic acids an extremely large genus of polymorphic variants of the TIM-1 gene with any nucleotide content (A or G or C or T) at any position within the TIM-1 gene. The examiner acknowledges that the claims require polymorphisms within or

specific to TIM-1 gene however this large genus of nucleic acids, polymorphic variants of TIM-1 gene and their association with atopy, is not described in the specification.
The specification merely discloses one polymorphism,157insMTTTVP, associated with protection against but not diagnostic of atopic immunological conditions, which is not a representative number of the large genus of TIM-1 polymorphisms. Furthermore the one polymorphism, 157ins MTTTVP disclosed by the specification is not associated with atopic immunological conditions in all populations. Therefore the specification has not described a representative number of polymorphic species of TIM-1 gene that are associated with atopy

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

12. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAE BAUSCH whose telephone number is (571)272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Sarae Bausch/
Examiner, Art Unit 1634